A FACILE SYNTHESIS OF THE SUBSTITUTED TETRAHYDRONAPHTHALENES BY THE BENZO-PETERSON REACTION

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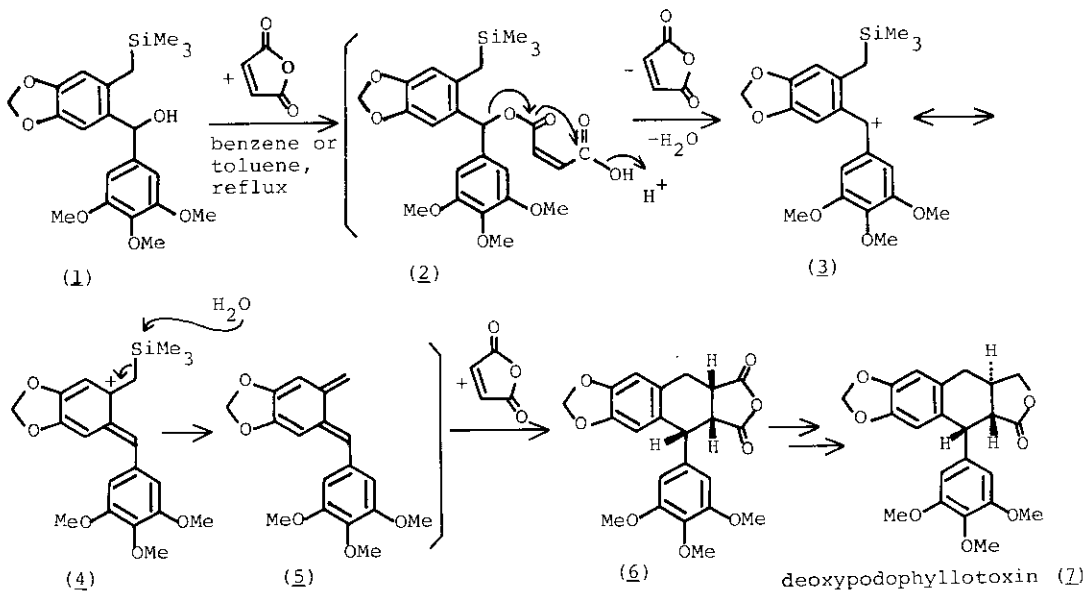
Abstract —— Thermal treatment of the o-hydroxymethylbenzylsilanes with an excess maleic anhydride or 2,3-dichloromaleic anhydride afforded the corresponding substituted tetrahydronaphthalenes stereoselectively in satisfactory yields presumably via the o-quinodimethane intermediates generated by the benzo-Peterson reaction.

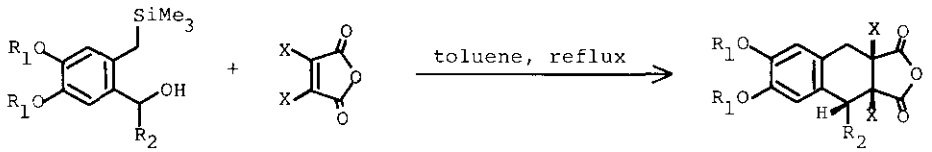
o-Quinodimethanes are very important intermediates for the synthesis of polycycles.[1-3] This stimulates the development of various methods for generating these reactive species.[3,4] We recently reported[5] an efficient stereoselective synthesis of an antitumor lignan lactone deoxypodophyllotoxin (7) from the o-hydroxymethylbenzylsilane (1) in which we proposed a generation of an o-quinodimethane intermediate (5)



Scheme 1

via the unprecedented benzologue of the Peterson reaction[6,7] in the key stage. Spontaneous generation of the o-quinodimethane (5) and its addition to maleic anhydride occurred smoothly by heating the o-hydroxymethylbenzylsilane (1) with five equivalents of maleic anhydride in benzene or toluene to produce stereoselectively the 1,2,3-trisubstituted tetrahydronaphthalene (6) in good yield (Scheme 1). In the present report we describe the synthesis of some substituted tetrahydronaphthalene derivatives (10) extending the benzo-Peterson method to other o-hydroxymethylbenzylsilane derivatives (8)[8].

Clean and smooth cycloaddition occurred when the benzylsilanes (8) were heated with five equivalents of maleic anhydride (9 : X=H) or 2,3-dichloromaleic anhydride (9 : X=Cl) in toluene at refluxing temperature to give rise to the corresponding substituted tetrahydronaphthalenes (10)[8] stereoselectively in acceptable yields (Scheme 2 and Table 1). Stereochemistry of the adducts (10 : R_2=Ar, X=H) was easily determined



(8) (9) (10)

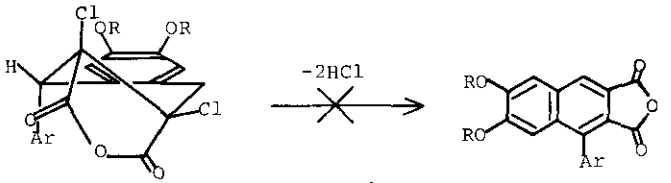
R_1=CH_3- or -CH_2-; R_2=H, 3,4-$(CH_3O)_2C_6H_3$, 3,4-(-OCH_2O-)C_6H_3, or 3,4,5-$(CH_3O)_3C_6H_2$; X=H or Cl

Scheme 2

Table 1

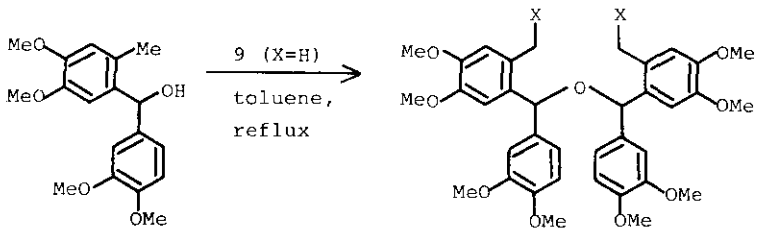
10	R_1	R_2	X	yield(%)	mp(°C)	^{1}H-nmr(δ)(ppm)($CDCl_3$)
a	Me	H	H	67	145-147	3.85(s,6H),6.67(s,2H)
b	Me	H	Cl	52	amorphous	3.25-4.05(2d,17Hz,4H),3.85(s,6H),6.65(s,2H)
c	Me	3,4,5—$(MeO)_3C_6H_2$	H	72	amorphous	3.73(s,6H),3.8(s,6H),3.85(s,3H),4.37(d,5.5Hz,1H),6.37(s,2H),6.63(s,1H),6.73(s,1H)
d	Me	"	Cl	57	amorphous	3.35-4.17(2d,17Hz,2H),3.75(s,6H)
e	Me	3,4—$(MeO)_2C_6H_3$	H	66	amorphous	3.8(s,6H),3.85(s,3H),4.58(s,1H),(s,1H),6.6(s,1H),6.7(s,1H) 3.80,3.87,3.88,3.93(each s,each 3H),4.4(d,5.5Hz,1H)
f	Me	"	Cl	56	amorphous	3.35-4.02(2d,16Hz,2H),3.73,3.83,3.9,3.93 (each s,each 3H),4.75(s,1H),6.53(s,1H),6.67(s,2H),6.75(s,2H)
g	Me	3,4—(-OCH_2O-)C_6H_3	H	67	174-175	3.78(s,3H),3.97(s,3H),4.25(d,5.5Hz,1H),6.0(s,2H)
h	Me	"	Cl	65	amorphous	3.43-4.25(2d,17Hz,2H),3.8(s,3H),3.97(s,3H),4.77(s,1H),6.0(s,2H)
i	-CH_2-	3,4,5—$(MeO)_3C_6H_2$	H	63	182.5-183.5	3.8(s,6H),3.85(s,3H),4.3(d,5.5Hz,1H),5.92(s,2H),6.5(s,2H),6.62(s,1H)
j	-CH_2-	"	Cl	51	194-195	3.3-4.1(2d,17Hz,2H),3.8(s,6H),3.85(s,3H),4.62(s,1H),5.95(s,2H) 6.35(s,2H),6.53(s,1H),6.71(s,1H)
k	-CH_2-	3,4—$(MeO)_2C_6H_3$	H	72	amorphous	3.8(s,3H),3.86(s,3H),4.32(d,5.5Hz,1H),5.9(s,2H)
l	-CH_2-	"	Cl	52	amorphous	3.15-4.0(2d,16Hz,2H),3.82(s,3H),3.86(s,3H),4.6(s,1H)

to have all cis configuration based on H_1-H_2 coupling (J=5.5 Hz) in ^{1}H-nmr spectra,[9] while the stereochemistry of the dichloro-adducts (10 : R_2=Ar, X=Cl) was also deduced to have cis-1(H)/2(Cl)-cis-2(Cl)/3(Cl) configuration since no 1-arylnaphthalenes (12) were formed under basic conditions due to their rigid conformation (11) unsuitably disposed to trans-dehydrochlorination (Scheme 3). The trimethylsilyl group was essential to form the cycloadducts (10) as only the benzylhydryl ether (14) was generated in moderate yield when the benzyhydrol ether (13) having no trimethylsilyl group reacted with maleic anhydride under the same conditions (Scheme 4).



(11) Scheme 3 (12)

The reaction of the benzylsilanes (8) with other dienophiles, such as dimethyl maleate, dimethyl fumalate, 2-butenolide, ethyl acrylate, and N-carbethoxymethyleneimine,[10,11] did not furnish cycloadducts under thermal conditions even in the presence of dehydrating catalysts, such as p-toluenesulfonic acid, pyridinium p-toluenesulfonate, acetic anhydride, or phthalic anhydride. The other catalysts, either acids ($SnCl_4$ or BF_3 Et_2O) or bases (KH or n-BuLi) which promote the normal Peterson reaction,[6,7] were also found to be ineffect. Furthermore, the fluoride catalysts (CsF or n-$Bu_4N^+F^-$) which initiate generation of o-quinodimethane from the benzylsilanes possessing a leaving group on the o-carbon atom,[4,12,13] were also found to be ineffective. In most cases only isolable compounds were determined to have the benzhydryl ether framework (15) with the silyl groups intact.



(13) (14) X=H (15) X=Me_3Si

Scheme 4

The general procedure for the synthesis of the starting o-hydroxymethylbenzylsilanes (8) and the formation of the substituted tetrahydronaphthalenes (10) was exemplified as follows. To a stirred solution of

2-bromo-4,5-dimethoxybenzyltrimethylsilane[14] (1.0 g, 3.3 mmol) in tetrahydrofuran (15 ml) was added butyllithium (15% (w/w) in hexane, 2.02 ml, 3.3 mmol) dropwise at -78 °C and after 15 min was added 3,4,5-trimethoxybenzaldehyde (0.65 g, 3.3 mmol) in tetrahydrofuran (15 ml) dropwise at the same temperature. After having completed (ca. 30 min) the reaction, the mixture was poured into water and was extracted with ether. The extract was washed with brine, dried ($MgSO_4$), evaporated, and purified (SiO_2 column, hexane-ether, 2:3 v/v) to give 2-[1-hydroxy-1-(3,4,5-trimethoxyphenyl)methyl]-4,5-dimethoxybenzyltrimethylsilane (8 : R_1=Me, R_2=3,4,5-trimethoxyphenyl) (1.15 g, 82.9%) as a colorless oil. This compound (150 mg, 0.38 mmol) was dissolved in toluene (10 ml) with maleic anhydride (9 : X=H, 188 mg, 1.92 mmol) and the mixture was refluxed for 24 h. The mixture was evaporated in vacuo to leave yellow residue which was purified (SiO_2 column, hexane-ethyl ether, 1:1 v/v) to give the substituted naphthalene (10 c, 117 mg, 72%) as a pale yellow non-crystalline foam.

In summary, the present result demonstrates that the benzo-Peterson method is very promising for the synthesis of the substituted tetrahydronaphthalenes by using maleic or 2,3-dichloromaleic anhydride as a dienophile though the addition with other dienophiles can not be achieved. We are currently extending the benzo-Peterson method to intramolecular fashion in order to trap less reactive dienophiles by constraining diene and dienophile in the same molecule.

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